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A NEW DISCOVERY,
A NEW COLLABORATION

The recent discovery of the JAK2 mutation in patients with MPDs has ignited major activity in the science and treatment of these diseases. The MPD Foundation is working with leading physicians, researchers and others in the MPD community to form a common front to share information, accelerate seminal discoveries and translate them as quickly as possible into patient benefits. We are working out the details and will share them as soon as we can. Our objective is to help all patients with or without the JAK2(V617F) mutation.

Meanwhile our researchers are making strong progress in their scientific investigations. Dr. Mesa has published at least 9 articles based on our grant and submitted numerous others for ASH abstracts. Dr. Moliterno, after only one year’s work, has published an article based on research that was fully funded by the MPD Foundation and recently submitted an abstract for the ASH conference later this year. Dr. Yang at Baylor has published 5 papers and several abstracts, and submitted 4 other papers for publication based on research performed with our grant.

$4 Million
raised for MPD research
to date!

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At the MD Anderson Cancer Center we are working to develop a comprehensive approach to understanding the biology and development of effective therapies for MPD. Our major focus is on clinical protocols with novel agents developed specifically for patients with MPD.

Our goals also include dissemination of information and education about MPDs, creation of an MPD Internet site, and an MPD newsletter for patients, families and healthcare providers.

**Current Clinical Trials**

We are currently recruiting patients for a number of clinical protocols for patients with myelofibrosis (MF), essential thrombocythemia (ET), and polycythemia vera (PV).

**Pegylated and Oral Interferon-alpha (IFN-α) for Patients with ET and PV**

Toxicity is the major obstacle in the use of IFN-α therapy. Most patients experience flu-like symptoms such as fatigue, fever, chills, headaches, lowering of blood cell count, and disturbances of the gastrointestinal tract and musculoskeletal system.

Different preparations of IFN-α are now available. Pegylated interferon, Pegasys, requires only one injection a week. That makes it more convenient to use, and the toxicities are less severe than with older forms of IFN. We are currently evaluating Pegasys in a phase II study for ET and PV patients.

We are also evaluating a new, oral form of IFN-α as a therapy for patients with PV and ET. There are virtually no side effects associated with interferon in this form, and significant efficacy has been observed in patients with Sjögren’s syndrome and other autoimmune and viral diseases. Our Phase II study is set to open for patients with ET and PV during the fall of 2005.

**Gleevec for Patients with PV**

Gleevec (imatinib mesylate) is a potent and selective tyrosine kinase inhibitor that interferes with the cell’s ability to replicate – thus preventing proliferation. Its efficacy in chronic myeloid leukemia is well-recognized. Currently, we are conducting a phase II trial of Gleevec in patients with PV.

We have noted responses in some patients, including a reduction or elimination in phlebotomy requirements, reduction or elimination of the use of Hydrea and/or Anagrelide, reduction or complete resolution of splenomegaly, normalization of bone marrow, and improvement in clinical symptoms such as pruritus, fatigue, headache, muscle and joint pain. The study is still open to a limited number of new patients.

**Vidaza (azacitidine) for MF**

Vidaza is a drug designed to modify the expression of certain genes in cancer cells, allowing them to become active in suppressing tumor growth (tumor suppressor genes). Preliminary results by several research groups showed that silencing of tumor suppressor genes is a common event in MF. Therefore, we have developed a Phase II study in MF using Vidaza, a drug that is currently approved as a therapy for myelodysplastic syndrome, a disease related to MF. The study is currently open and accruing patients.

**Combination of Targeted Agents as Therapy for MF: PTK787 and Gleevec**

Abnormal levels of angiogenesis (new blood vessel formation) and circulating angiogenic factors have been documented in patients with MF. We are studying the use of PTK787, a potent oral angiogenesis inhibitor, in combination with Gleevec (imatinib mesylate), which acts against other receptors that are possibly important in the pathophysiology of MF. Because the agents target different factors, we believe that the use of the combination might increase the benefits derived. We are currently accruing patients in a clinical study of PTK787 and Gleevec for patients with MF.
FOCUS: HOW DO MPD’S AFFECT YOUR QUALITY OF LIFE?

By Ruben Mesa, MD
Associate Professor of Medicine
Division of Hematology
Mayo Clinic

As a community of physicians, my colleagues around the world and I have many simultaneous goals in trying to help MPD patients.

The first, of course, is to try to find a cure for what is probably a range of similar disorders. Accomplishing this will need a good understanding of the cause; hopefully we are making strides in that regard with the exciting information learned this year about the role of JAK2 mutations in these diseases.

Our second goal is to try to treat people today the very best way we can. This includes the full spectrum of available therapies including aspirin, phlebotomy, oral chemotherapy (hydroxyurea, thalidomide, anagrelide), injectable chemotherapy (interferon, cladribine, leukemia level induction), surgical procedures (splenectomy), radiation, and bone marrow transplant (full, mini, etc.). The choice among these non-specific therapies is rarely ideal.

Our third goal is to perform clinical trials to evaluate new drugs that we hope will better control the diseases (especially in the more severe phases), based on what we have learned from drug activity in related diseases (revlimid, bortezomib, and thalidomide combinations) or our increased understanding of the molecular causes of the diseases (future JAK2 inhibitors.)

The Overlooked Issue: Quality of Life

Despite all these efforts, many patients with MPDs suffer a decrease in quality of life from a variety of factors that are not currently being well addressed. Specifically, disease (and medication) related fatigue remains an elusive area for improvement.

(continued on page 5)
THE JAK2 MUTATION: SUSPICIONS CONFIRMED, SURPRISES REVEALED

By Alison Moliterno, MD
Assistant Professor
Department of Medicine, Division of Hematology
Johns Hopkins University

The discovery of the JAK2 gene mutation (JAK2 V617F) ushers in a new era of scientific investigation, diagnosis and treatment of the chronic myeloproliferative disorders (MPD). In the few months since the initial reports of the mutation, seven laboratories from Europe and the United States have confirmed the association of the JAK2 V617F mutation with these disorders.

Investigators have observed many striking features of the mutation and its relationship to the MPD. These features have both confirmed what we have always suspected in the MPD and have surprised us with what we did not expect.

The Traditional Approach to CMPDs

For more than 50 years we have defined polycythemia vera (PV), idiopathic myelofibrosis (IMF) and essential thrombocytosis (ET) on the basis of clinical and laboratory features. The criteria for diagnosis of these disorders were subjective in the sense that the diseases were defined by criteria determined by committees of physicians. This is problematic, as many patients don’t fulfill all of the clinical criteria and yet may still have the disease, and many patients can inadvertently fulfill criteria without really having the disorder.

PV, ET and IMF have much in common with regard to their respective disease phenotypes, or how patients manifest their clinical symptoms, laboratory changes and the appearance of the bone marrow under the microscope. Since PV, ET and IMF share common clinical and laboratory findings, frequently doctors cannot determine which of these an individual patient really has, or even sometimes whether they actually have a MPD or some other reason for changes in their blood counts.

In addition, the type of MPD in a single patient can change, sometimes within the first few months of the diagnosis, and sometimes after decades, further demonstrating our lack of diagnostic accuracy and our comprehension of these disorders. Thus we had always suspected that PV, IMF and ET were related in their cause. Finding JAK2 V617F in all three disorders therefore in a sense is not a surprise given what we have observed for decades with regard to their similar clinical features.

“How can a single gene mutation generate such different diseases amongst individuals?”

One Mutation, Three Diseases: What’s Really Going On?

On the other hand, how can a single gene mutation generate such different diseases amongst individuals? Given the variability within the MPD, most investigators have postulated that many different genetic changes were necessary to explain the variation we observe within individuals with similar appearing disorders.

However, investigators have found that approximately 90% of patients with PV, 40% of patients with ET, and 50% of patients with IMF have the identical JAK2 mutation, and that the mutation is found in some patients with quite different bone marrow disorders such as sideroblastic anemia, chronic neutrophilic leukemia and others.

Finding the exact same gene mutation in patients with different types of MPD was a surprise. This conundrum is encountered often in medicine, and we have learned that in most diseases, many genetic influences are at play in generating the disease type in individual patients, even though they may all share a single identical mutation. The other genetic changes that determine the disease type in an individual may include other acquired gene changes in addition to the JAK2 mutation or may be part of the patient’s own inherited genetic make-up when they acquire the JAK2 mutation.
Despite the Questions, a Real Breakthrough

The JAK2 mutation is a true breakthrough on many levels. Often patients do not have the full manifestations of a myeloproliferative disorder, so that finding a positive test for the JAK2 mutation will help establish an MPD earlier than possible and with much less insecurity. Armed with the knowledge of the JAK2 mutation status of patients enrolled in clinical trials, physicians will be better able to compare patients and monitor the effect of treatments. Having knowledge of this genetic mutation will also help clinicians better follow patients, anticipate complications, and determine which kinds of therapy really make the disease go away, and which just control blood counts.

Absence of the JAK2 mutation, however, does not rule out a myeloproliferative disorder. In patients who still fit the clinical criteria for an MPD, but do not have the JAK2 mutation, there may be other genetic changes that mimic the effect of the JAK2 mutation on the growth of blood cells and thereby produce similar clinical disorders.

By studying the effect of the JAK2 mutation on blood cell growth, we will identify important molecules and pathways that will shed light on both JAK2 positive and JAK2 negative MPD. Importantly, the benefits of therapeutics designed to specifically inhibit the JAK2 mutation may be applicable to patients without the JAK2 mutation if these agents inhibit important growth pathways that are commonly disturbed in both JAK2 positive and JAK2 negative MPD patients.

We have seen this scenario demonstrated recently by the clinical studies that have shown a beneficial effect of Gleevec in patients with PV. Despite its ability to specifically inhibit the molecular lesion that causes chronic myelogenous leukemia, Gleevec is also effective in many patients with PV, presumably due to its inhibition of growth pathways that are also altered in PV.

The challenges that face the MPD community now are to understand the relationship of the JAK2 mutation to the development of the clinical disorders and to develop therapies specific to these disorders. The fact that so many research laboratories are reporting results so quickly really reflects the cooperation between international research groups, the support of the MPD Foundation, and the cooperation of MPD patients, all of which are essential in conquering these diseases.

Many years ago a scientist told me that the real research in MPD will start when their cause is unveiled. Truly, we are at the beginning of the beginning.

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FOCUS: HOW DO MPD’S AFFECT YOUR QUALITY OF LIFE?
(continued from page 3)

We have therefore decided to try to bring the issue of MPD quality of life (QOL) to the forefront, so that this can be considered and targeted in parallel with other features of the diseases.

We have set out on a multi-phase program to address this issue. The first is to help to define the extent and range of MPD effects on QOL through an Internet-based survey. The second is to design clinical trials specifically targeting disease-related fatigue. The last is to try to include QOL measurements as part of future MPD trials to learn how much new agents help (or not) in terms of quality of life.

National Web-Based Survey of MPD QOL Issues

There is no one universal type of patient with these diseases (ET, PV, or IMF). Readers of this newsletter will range from their 20s all the way to their 80s. Some have never really had many symptoms from their disease, while others have been hospitalized for severe complications.

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GOING THE DISTANCE FOR A FRIEND

Jeff Birkel Runs the Boston Marathon to Honor His Friend and Colleague Dave Kettler and Raise Funds for the MPD Foundation

Jeff Birkel and Dave Kettler have been friends for 20 years. Dave has an MPD, and Jeff decided to do what he could to help raise funds for research. He’s a marathon runner, so this past April 18 he ran the Boston Marathon – going every step of the way for Dave. Here’s his story of the race.

Let me begin by thanking all of our friends who pledged a donation to the MPD Foundation in Dave’s honor. Your response and generosity have been overwhelming and nothing short of fantastic. Thanks to all of you, we’ve raised $5148.20 for the Foundation!

The race started right on time and for the first mile or so, I really had to watch my step as it was quite crowded. The first six miles are mostly downhill, but there were periods of up then down, then back up and down some more. Now, everyone that I talked to that had run the race before said not to run this first downhill bit too fast as it will wreck your thighs. I followed their advice and ran a steady pace that I thought I could hold for the duration.

The next nine miles are basically at the same elevation, but it seemed I was either going up slightly or going down slightly, sort of undulating. Again, I ran a steady pace, something which I thought I could maintain.

Trouble at 14 Miles

Pretty much from there though, things started to get difficult. Shortly before the 14 mile mark I began to notice that my thighs were hurting. I knew this was not a good sign – nothing should be hurting yet! I decided that I’d better slacken my pace slightly, especially since it was only just over a mile until I began the big five mile climb cumulating at the crest of Heartbreak Hill.

Just then I got a cramp in my side. Things definitely were not going to plan! For the next four miles or so I was pretty miserable, but I kept reminding myself that I would likely be talking to Dave about how the race went and I just couldn’t bear the thought of telling him I had to quit or even had to walk. He never gave up last winter when he was at his lowest and I drew strength from that.

Over the Line in 3:16:00!

After mile eighteen, the cramp went away and I pretty much got into a zone and ran the next eight miles without incident. I will say though that my first thought as I crossed the line was “The pain is finally over!” Of course, I’m already planning my next marathon, likely Chicago in October.

For those of you who like statistics, I finished 1886 overall out of a field of 20,500 – 1749th in my gender category and 459th in my age group (40 to 50). My time to complete the 26.2 miles was 3:16:00. It took me four days before I could walk normally again!

Running the Boston Marathon was a special time for me, and it was great to be a part of something with so much tradition. But what made it memorable was the privilege of running to honor Dave and his fight for life, and the overwhelming support from so many of our friends.
Therefore, as a community you have a broad range of needs and hopes. In an attempt to define the extent and range of MPD impact on fatigue and QOL, researchers from Mayo, Harvard, MD Anderson, and the CMPD Education Foundation (with the help of Joyce Niblack, JD and an MPD patient) constructed an Internet survey. The survey addresses disease characteristics, current fatigue levels, impact of the MPD on QOL, current physical activity levels, and limiters to physical activity (from the MPD, other unrelated diseases, or medications.)

**Goals of the Survey**

Our hopes in collecting this data are several. First, to demonstrate the unity of the MPD community and your desire to work together with investigators to make a difference in these diseases. Second, to fully define the extent and range of impact of MPDs on patients’ QOL. We hope this information will further support the efforts to combat these diseases.

Finally, we want to establish a firm baseline on the effect of MPDs on QOL so researchers can analyze new therapies, as they become available, to see if they actually improve the quality of patients’ lives as well as the results of their laboratory tests.

**The MOVE Trial**

We believe that structured, measured, and appropriate increases in physical activity will benefit MPD patients, and we are planning to study that hypothesis with the MOVE trial (Myeloproliferative patients Overcoming fatigue with structured Voluntary Exercise.)

**The aims of the trial are:**

- Conduct a single arm trial (MOVE Trial) of increased, and guided, physical activity in patients with MPDs to assess improvements in fatigue through validated instruments of fatigue measurement
- Assess the effect of participation in the MOVE Trial on validated quality of life (QOL) measurements
- Assess the effect of participation in the MOVE Trial on objective physiologic measurements of both fitness and baseline disease features

The MOVE trial represents a novel and concerted effort to explore exercise as a form of chronic disease management, and to try to improve the QOL of MPD patients through a complementary therapy for a disease-associated toxicity (fatigue), which has not responded to pharmacologic interventions.

If you suffer from fatigue, you are probably asking yourself, “Is Dr. Mesa crazy? I feel lousy! How am I going to be able to exercise?” MPD patients range from those of you who run marathons, but have a harder time training because of iron deficiency, to those who have fatigue walking to the kitchen. You have limitations ranging from none to large spleens, neuropathy from medications, or even other illnesses.

What we are proposing is, first, that there are more ways to try to feel better than simply taking additional medications, and, second, that a guided and individualized increase in physical activity is likely to benefit the majority of MPD patients.

Initially we are looking at a walking-based program where a structured increase in activity (as measured by pedometer) is individualized by a Physical Medicine Physician and Physical Therapist. This will occur in conjunction with whatever baseline medical management is ongoing for an individual’s MPD. If successful, we hope that this will be the first in a series of trials looking at complementary (non medicine-based) therapies to be used alone or in conjunction with future experimental drug trials.

**Looking Ahead**

I feel that the future for MPD patients is bright. Greater understanding of the cause of the diseases will hopefully lead to effective targeted therapies. The hope is to better understand the true spectrum of the burden that MPDs place on patients, and to devise comprehensive strategies to address the full range of symptoms and problems these diseases cause. I look forward to continuing to work closely with the MPD community to try to address these issues and to improve MPD QOL.
ENCOURAGING WORDS FROM THE MAYO CLINIC

Ruben Mesa, MD
Associate Professor of Medicine
Division of Hematology, Mayo Clinic

This past year has seen an explosion in new information regarding the pathogenesis of the MPDs with the discovery of the activating point mutation V617F in JAK2. We were integrally involved in these initial studies through our collaboration with the group of Dr. D.G. Gilliland at Harvard.

The wonderful support from the MPD Foundation has allowed us to try to quickly determine the clinical importance and many of the biological significances of a JAK2 mutation in MPD patients.

Additionally, we continue, with the help of the MPD Foundation, to actively screen a wide array of potentially active therapeutic agents for MMM, including CC-5013 (Revlimid), Arsenic Trioxide, Seocalcitol, Bortezomib (PS-341), Adaphostin, R115777 (tipifarnib), CCI-779, and inhibitors of VEGF (vascular endothelial growth factor). Preliminary results suggest potential benefits from some of these agents.

JANE SHAFER BEQUEST:
An Important Gift, at a Key Moment in MPD Research

We recently learned that we have been named as the principal beneficiary of the estate of Jane Shafer of Tucson, Arizona, who died in May of this year. Jane asked that she be remembered in the newsletter, and we are happy to commemorate her generosity and to publicly thank her and her family and friends for this gift.

Hers was a restricted gift to be applied towards MPD research into the cause, cure and treatment of MMM and other myeloproliferative disorders and it comes just in time to support researchers as they continue to endeavor to understand the genetic causes of the MPD’s, particularly in light of the JAK2 discovery.

We are sad to hear of the loss of one of our community, yet appreciative of the opportunity she has afforded us to promote research as we enter the new phase of MPD discovery and investigation. We promise that her contribution will be used in an effort to benefit every one of us in the MPD community.

For further information on how to name the MPD Foundation in your will, please go to the MPD Foundation website at www.mpdfoundation.org, or email Robert Rosen at: rrosen@mpdfoundation.org

For more information or to make a donation, contact the MPD Foundation at:

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MPD Foundation Update is a periodic newsletter published by the MPD Foundation to provide members of the MPD community with information on current research and the Foundation’s activities.

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